IFW

Docket No.: C15043/91752CON1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Continuing Application of :	)	
Paul N. HOLVOET and Désiré J. COLLEN	)	Parent Examiner: L. Cook
Serial No.: 10/802,643	)	Expected Art Unit: 1641
Filed: March 17, 2004	)	
For: ASSAYS, ANTIBODIES, AND STANDARDS FOR DETECTION OF OXIDIZED AND MDA-MODIFIED LOW DENSITY LIPOPROTEIN	)	

THIRD SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Mail Stop Amendment
Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants wish to make of record the three documents identified below (clean copies and a Form PTO-1449 listing them are enclosed). **Applicants believe that that no fee is required for this paper** (see last paragraph).

160. Holvoet P. "Oxidized LDL And Coronary Heart Disease," *Acta Cardiol.* 2004 Oct; 59(5): 479-484.

161. Cesari M, Kritchevsky SB, Nicklas BJ, Penninx BW, Holvoet P, Koh-Banerjee P, Cummings SR, Harris TB, Newman AB, Pahor M. "Lipoprotein peroxidation and mobility limitation: results from the health, aging, and body composition study," *Arch Intern Med.* 2005 Oct 10; 165(18): 2148-2154.

162. Meisinger C, Baumert J, Khuseyinova N, Loewel H, Koenig W. "Plasma oxidized low-density lipoprotein, a strong predictor for acute coronary heart disease events in apparently healthy, middle-aged men from the general population," *Circulation*. 2005 Aug 2; 112(5): 651-657 (Epub 2005 Jul 25).

REMARKS

The relevance of these items is set forth below.

160. Holvoet P. "Oxidized LDL And Coronary Heart Disease," *Acta Cardiol.* 2004 Oct; 59(5): 479-484, concerns OxLDL and coronary heart disease. The abstract reads in part as follows. "Lipid oxidation results in the generation of aldehydes that substitute lysine residues in the apolipoprotein B-100 moiety. Lipid together with protein oxidation in LDL results in the generation of oxidized LDL. We, among others, have demonstrated an association between coronary heart disease (CHD) and increased plasma levels of oxidized LDL. Recently, we have demonstrated a higher prevalence of elevated oxidized LDL in persons with high-calculated CHD risk prior to events. The odds of having elevated oxidized LDL for persons with high-calculated CHD risk prior to events were even higher than for persons with diagnosed CHD. A likely explanation is that once CHD has been diagnosed the patients are more treated with a statin that appears to decrease oxidized LDL even beyond its cholesterol-lowering effect. We have identified several metabolic syndrome components (high triglycerides, low HDL-cholesterol, glucose intolerance and diabetes) that independently of LDL-cholesterol, predicted high levels of oxidized LDL. Finally, elevated oxidized LDL predicted myocardial infarction in the Health ABC cohort consisting of well-functioning elderly people, even after adjusting for age, gender, race, smoking, and the metabolic syndrome." The use of monoclonal antibody mAb-4E6 is discussed at pages 479-480. "Figure 1 compares representative receiver operating characteristic [ROC] curves of oxidized LDL and the total-to-HDL-cholesterol ratio for CHD" (page 480).

161. Cesari M, Kritchevsky SB, Nicklas BJ, Penninx BW, Holvoet P, Koh-Banerjee P, Cummings SR, Harris TB, Newman AB, Pahor M. "Lipoprotein peroxidation and mobility limitation: results from the health, aging, and body composition study," *Arch Intern Med.* 2005 Oct 10; 165(18): 2148-2154, concerns a study to assess the predictive value of a lipoprotein peroxidation marker, oxidized low-density lipoprotein (oxLDL), for incident mobility limitation (ML). The abstract reads in part as follows. "After adjustment for potential confounders (sociodemographic factors, smoking, physical activity, body mass index, clinical conditions, biological markers, and medications), the relationship between the oxLDL/LDL-C [LDL cholesterol] ratio and disability events was statistically significant .... CONCLUSIONS: Lipoprotein peroxidation predicts the onset of ML in older persons. The oxLDL predictive value for ML is partly explained by interleukin 6 levels." Monoclonal antibody 4E6 was used to measure plasma levels of oxidized LDL (page 2149). "On the basis of current evidence we may hypothesize that inflammation and oxidative damage, strongly related to each other, may represent promoters of the disabling process. ... A synergistic relationship between inflammation and oxidative damage can also be found at the beginning of several pathophysiologic changes and clinical conditions potentially mediating the onset of physical function loss" (page 2152; footnotes omitted).

162. Meisinger C, Baumert J, Khuseyinova N, Loewel H, Koenig W. "Plasma oxidized low-density lipoprotein, a strong predictor for acute coronary heart disease events in apparently healthy, middle-aged men from the general population," *Circulation.* 2005 Aug 2; 112(5): 651-657 (Epub 2005 Jul 25), concerns the use of oxidized low-density lipoprotein to predict acute coronary heart disease (CHD) events. The abstract reads in part as follows. "Oxidized LDL (oxLDL) is thought to play a key role in the inflammatory response in the arterial vessel wall. ... OxLDL was determined by ELISA in 88 men with incident CHD and in 258 age- and survey-matched controls. ... Plasma oxLDL was the strongest predictor of CHD events compared with a conventional lipoprotein profile and other traditional risk factors for CHD. When both oxLDL and C-reactive protein were simultaneously assessed in the same model, they still predicted future CHD events even after multivariable adjustment. CONCLUSIONS: Elevated concentrations of oxLDL are predictive of future CHD events in apparently

healthy men. Thus, oxLDL may represent a promising risk marker for clinical CHD complications and should be evaluated in further studies." "The aim of the present prospective, nested, case-control study therefore was to determine whether plasma oxLDL concentrations predict risk of acute CHD events. Furthermore, we sought to investigate whether measurement of plasma oxLDL in addition to a standard lipid profile and C-reactive protein (CRP), a sensitive marker of inflammation, might add to improved prediction of CHD risk" (page 651). Monoclonal antibody 4E6 was used to determine plasma concentrations of oxLDL (page 652). "There was no significant correlation between oxLDL and CRP in cases and only a barely significant association in controls" (*id.*). "Among all lipid variables, oxLDL was the most powerful predictor of risk in multivariable analysis ..." (page 653). "Furthermore, we investigated whether oxLDL would predict future CHD events independent of CRP and TC/HDL-C [total cholesterol/HDL cholesterol]. ... When assessed in a separate model (Figure 1), CRP was a powerful predictor in multivariable analysis .... However, oxLDL did not significantly increase the prediction of a coronary event. After inclusion of oxLDL in a model containing CRP, the TC/HDL-C ratio, and all other cardiovascular risk factors, the additional improvement in risk prediction was rather low ..." (page 654).

* * *

All three documents are believed to be of moderate relevance; however, the Examiner's independent consideration of these documents and of their relevance is respectfully requested. The Examiner is also requested to initial and return a copy of the accompanying PTO-1449 Form to evidence such consideration.

This THIRD SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT is being filed in accordance with the provisions of 37 CFR § 1.97(b)(3) based on applicants' belief that it is being filed before the mailing of a first Office Action

on the merits. Thus, **a fee is not required for filing this paper**; however, if any fee is owed, please charge the fee to our Deposit Account No. 02-4467.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Mail Stop Amendment, Commissioner For Patents, P.O. Box 1450, Alexandria, VA 22313-1450

on November 8, 2005
(Date of Deposit)

Stephen P. Gilbert
Signature

Respectfully submitted,

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Form PTO-1449 (Rev.)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: C15043/9175CON1	APPLICATION NO.: 10/802,643
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)		APPLICANT Paul N. Holvoet and Desire J. Collen	
		FILING DATE March 17, 2004	GROUP: 1641

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation	

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

			Holvoet P. "Oxidized LDL And Coronary Heart Disease," *Acta Cardiol.* 2004 Oct; 59(5): 479-484.
			Cesari M, Kritchevsky SB, Nicklas BJ, Penninx BW, Holvoet P, Koh-Banerjee P, Cummings SR, Harris TB, Newman AB, Pahor M. "Lipoprotein peroxidation and mobility limitation: results from the health, aging, and body composition study," *Arch Intern Med.* 2005 Oct 10; 165(18): 2148-2154.
			Meisinger C, Baumert J, Khuseyinova N, Loewel H, Koenig W. "Plasma oxidized low-density lipoprotein, a strong predictor for acute coronary heart disease events in apparently healthy, middle-aged men from the general population," *Circulation.* 2005 Aug 2; 112(5): 651-657 (Epub 2005 Jul 25).

EXAMINER	DATE CONSIDERED

Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.